## REMARKS

Claims 1–10, 31–40, 52 and 61–75 are pending in the present application. By this amendment, claims 4-6, 34-36, and 67-69 have been amended. Accordingly, claims 1–10, 31–40, 52 and 61–75 are currently under consideration. Applicant respectfully submits that these claims are allowable.

**Claim Rejections under 35 USC § 112 (second paragraph)**

Claims 3, 7, 10, 33, 40, 66, 70, and 73 and all claims dependent therefrom stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 7, 10, 33, 40, 66, 70, and 73 claims dependent therefrom include limitations related to *"$DF_2$."* Applicant respectfully submits that these limitations are not vague and indefinite. For example, claim 3 includes: *"$DF_2$ is a type 2 diabetes feature that represents an incidence of type 2 diabetes for the virtual patient."* That is, $DF_2$ characterizes whether or not the virtual patient has type 2 diabetes. For example, the embodiment discussed at paragraphs 162-163 of US 2005/0125158 A1, includes:

**[0162]** For type 1 diabetes, the feature $DF_1$ is a function of age, sex, family history, and race/ethnicity. For type 2 diabetes, the feature $DF_2$ is a function of age, sex, race/ethnicity, body mass index (BMI), and a factor that registers the effect of glucose intolerance. In an embodiment of the present invention, these formulas may be represented as follows

$$DF_1(t) = (1 - \exp(-\exp(a + bt + ct^2 + dt^3 + et^4 + ft^5)) \times famhis) / \xi_1$$

$$DF_2(t) = \left(1 - \exp\left(-u \times IGT(\xi_2) \Big/ \left(1 + \exp\left(-\frac{t - b}{c}\right)\right)\right)\right) \times RBMI(BMI) / \xi_2$$

**[0163]** Race/ethnicity and sex are included through the values of the parameters a, b, c, d, e, and f. These equations may be scaled so that a person first begins to develop symptoms when $DF_1 \approx 1$ or $DF_2 \approx 1$. $\xi_1$ is a random value drawn from a uniform distribution on the interval (0, 1) hereinafter denoted as U[0, 1]. Drawing $\xi_1$ from U[0, 1] will cause the individuals in a large population (of a particular race/ethnicity/sex) to get type 1 diabetes at rates that match the observed age-specific incidence rates for that population, while allowing every individual to have a unique history of diabetes, including never getting type 1 diabetes. Similar intervals may be used for other values of $\xi$. famhis registers a patient's genetic propensity to develop the disease, based on their family history. It is set at birth and does not change.

That is, $DF_2$ can be scaled so that $DF_2(t)=1$ indicates the onset (or incidence) of type 2 diabetes at time t (e.g., age t). In this context one can interpret the above formula for $DF_2$ as $DF_2(t) = dF_2(t)/\xi_2$, where $dF_2(t)$ characterizes the *average* incidence of type 2 diabetes for the population (e.g., the probability of having type 2 diabetes by age t) and $\xi_2$ provides a random selection from the population (e.g., $\xi_2$ is selected from U[0,1]). The above example is illustrative, and other quantitative characterizations of type 2 diabetes are also possible.

Claims 3, 8, 9, 33, 38, 39, 40, 66, 71, 72, and 75 include limitations related to parameters (e.g., a b, c, and d) and define them as being set to fit data for a population. Applicant has amended claims to clarify the appropriate distinctions between parametric limitations. Applicant respectfully submits that these limitations are not vague and indefinite. For example, claim 3 includes: *"the parameters a, b, c, and d are set to fit data for a population that is represented by*

*the virtual patient."* A population may be defined or characterized, for example as in the cited paragraphs 162-163 above, by "Race/ethnicitiy and sex" (as well as other characterizing features) and the virtual patient may be considered as a representative (or random selection) from the population. The parameters may be set by calculations based on data derived from the population (e.g., according to a *"least-squares criterion"* as further specified in claim 62), but alternatively other values may be used according to the requirements of the operational setting (e.g., testing through a range of parameter values).

Claims 4, 34, and 67 include limitations for *"random values."* Applicant has amended these claims to maintain consistency in the limitations. For example, claim 4 as amended includes limitations *"wherein $\xi_2$ and $\xi_3$ are random values selected from distributions for randomizing the virtual patient within the population."*

Claims 4, 34, and 67 and all claims dependent therefrom include limitations for "*randomizing the virtual patient within the population."* Applicant respectfully submits that these limitations are not vague and indefinite. For example, as discussed in the cited paragraphs 162-163 above, these limitations may relate to conventional randomizing processes (e.g., sampling from the uniform distribution U[0,1] or some other distribution).

Claims 6, 36, and 69 and all claims dependent therefrom include limitations for the *"the random value $\xi_3$."* Applicant has amended claims to clarify the antecedent basis of these limitations (e.g., in claims 4, 34, and 67 respectfully).

Claims 10, 40, and 73 and all claims dependent therefrom include limitations for the variable *"I"* on the left-hand side and the number *"1"* on the right-hand side. Applicant respectfully submits that these limitations are not vague and indefinite. Note that the variable *"I"* is further specified in claim 1, for example, as *"the virtual patient's insulin level (I)."* See also paragraph 291 of of US 2005/0125158 A1.

Claims 5, 35, and 68 include limitations for parameters in the formula for RBMI(BMI). Applicant has amended these claims to clarify the appropriate distinctions between parametric limitations.

Applicant respectfully requests that the above-cited rejection under 35 U.S.C. 112, second paragraph, be withdrawn.

**Claim Rejections under 35 USC § 103**

Claims 1–2 ,31–32, 52, 61, 63, 65, and 74 stand rejected under 35 U.S.C. 103(a) as being unpatentable over van Holde (1996). Applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (MPEP § 2143) Applicant respectfully submits that that the Examiner has failed to present a *prima facie* case of obviousness.

Not All Claim Limitations Taught or Suggested

Claim 1 includes limitations for *"calculating the virtual patient's FPG at time t by solving an equation* $FPG(t) = FPG_0 / (I * E)$." Applicant respectfully submits that the cited reference does not disclose or suggest these limitations and related limitations. In particular, the cited reference does not disclose or suggest quantitative characterizations generally or the specific limitations of the claims as applied to the quantitative characterizations.

Van Holde (1996) does not disclose or suggest quantitative characterizations generally. As noted in the Office Action, "Van Holde (1996) at page 824–825 teaches the role of insulin in the blood." However, as also noted in the Office Action, "Van Holde (1996) does not explicitly teach calculating the level of blood glucose according to the equation as is instantly claimed." In

fact, there are no quantitative characterizations that can be related or identified with the limitations of the invention as claimed by claim 1. The Office Action points out only that "Van Holde (1996) at page 824–825 teaches the role of insulin in the blood," and "Van Holde (1996) at page 826–827 further teaches the relationship between blood glucose levels and insulin levels, such as if you increase insulin levels then blood glucose levels decrease and vice versa under normal circumstance."

Van Holde (1996) does not disclose or suggest specific limitations related to the quantitative characterizations. In particular, Van Holde (1996) does not disclose or suggest limitations for *"Fasting Plasma Glucose"* which relate to a more specific characterization than simply "glucose level in the blood." For example, paragraph 169 of US 2005/0125158 A1 includes:

> **[0169]** In the progression of diabetes, the development of signs, symptoms, and complications, and the response to treatments are determined primarily by the steady state level of glucose, which can be represented either by the fasting plasma glucose or $HbA_{1c}$. In the model, the FPG in a person with diabetes is determined by six variables that represent: the average FPG in people who do not have diabetes; hepatic glucose production; the effect of insulin resistance on hepatic glucose production; the insulin amount (I); the efficiency with which the body (liver, muscle, and fat) uses insulin (E); and the two primary diabetes features ($DF_1$ and $DF_2$). In people who develop type 2 diabetes, the simulated liver cells develop a resistance to the effects of insulin. This causes the simulated liver to produce too much glucose. In response, the simulated beta cells produce more insulin. Over time, this compensatory mechanism begins to fail, through a combination of decreased insulin production (e.g., "beta cell fatigue"), and increasing resistance to insulin by the liver. In addition, the uptake of glucose by the simulated muscles and fat gradually decreases due to insulin resistance affecting those organs. Taken together, these factors create a relative deficiency of insulin, with resulting increases in glucose. In an embodiment of the present invention, these relationships may be addressed as follows.

The cited reference contains no disclosure directed towards *"Fasting Plasma Glucose(FPG)"* (e.g., as a characterization of "the steady state level of glucose") together with

related quantities *"basal hepatic production ($FPG_0$),"* *"insulin level (I),"* *"efficiency of insulin use"* *"E"*, for *"outputting at least one value for the virtual patient's FPG at time t to a user."*

Applicant respectfully submits that the Examiner has improperly relied upon inherency in support of the rejection. Reliance on inherency when the reference is silent about the asserted inherent characteristic requires a rationale or evidence showing inherency. MPEP § 2112. The rationale or evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." In re Robertson, 169 F.3d 743, 745 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999); (MPEP § 2112>IV).

Improper Combination or Modification of References

According to the Office Action, "It would have been obvious to one of ordinary skill in the art to mathematically represent the calculation of a fasting blood glucose level as being indirectly proportionate to the level of insulin as Van Holde (1996) has clearly described in the recited pages. It has been well known by those of ordinary skill in the art that under normal circumstances, if one increases the level of insulin in the blood that its effect is to decrease the glucose level in the blood. It is common to those of ordinary skill in the art to represent such relationships generically and mathematically as an indirect relationship." (emphasis added)

As discussed above, the rejection ignores limitations of the claims (e.g., *"Fasting Plasma Glucose(FPG)"*) and provides no motivation for modifying the reference to achieve the invention as claimed. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. (MPEP 2143.01)

In this case, the rejection relies on "common knowledge" without any apparent support. It is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record as the principal evidence upon which a rejection is based. "[T]he Board cannot simply reach conclusions based on its own understanding or experience -- or on its

assessment of what would be basic knowledge or common sense. Rather, the Board must point to some concrete evidence in the record in support of these findings." (*In re Zurko*, 258 F.3d 1379, 1385 (Fed. Cir. 2001)) (MPEP 2144.03)

No Reasonable Expectation of Success

According to the Office Action, "It has been well known by those of ordinary skill in the art that under normal circumstances, if one increases the level of insulin in the blood that its effect is to decrease the glucose level in the blood. It is common to those of ordinary skill in the art to represent such relationships generically and mathematically as an indirect relationship." (emphasis added)

Applicant respectfully submits that a general understanding of behavior "under normal circumstances" together with general principles "to represent such relationships generically and mathematically" provides no reasonable expectation of success for the modifications proposed with respect to this rejection. The Examiner has not demonstrated a "degree of predictability" sufficient to support this rejection. (MPEP 2143.02)

Conclusion

The above-cited characteristic features of the present invention as claimed by claim 1 are not disclosed or suggested by the cited reference. Therefore, claim 1 is allowable over the cited reference. Claims dependent from claim 1 are likewise allowable over the cited reference. Corresponding apparatus claims are likewise allowable including claim 31 and its dependent claims. Corresponding program storage device claims are likewise allowable including claim 52 and its dependent claims.

Further, claim 2 includes limitations *"wherein E is scaled such that E = 1 in the absence of diabetes and 0≤E<1 in the presence of diabetes."* As discussed above with respect to claim 1, the cited reference does not disclose or suggest this limitation. For example the Office Action does not point out any quantitative characterization of efficiency or even any specific discussion

of efficiency in the cited reference. Similar arguments apply for related limitations in apparatus claim 32 and program storage device claim 65.

Applicant respectfully requests that the above-cited rejection under 35 U.S.C. 103(a) be withdrawn.

## CONCLUSION

In view of the above, Applicant respectfully submits that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 14-1437** referencing Docket No. 8223.002.CPUS02. However, the Commissioner is not authorized to charge the cost of the issue fee to said Deposit Account.

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